

Nanotechnology-Based Vaccines

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Abstract

Several new infectious diseases have developed in recent years, and a few old ones that were formerly thought to pose no threat to humans have made a comeback. Millions of fatalities are attributed to these illnesses together, having a significant negative influence on the worldwide socioeconomic and healthcare sectors. The lack of appropriate medications for many of these disorders is one of the biggest obstacles to treating them. Yet, several of the most common diseases currently have no vaccinations that are reliable. The ideal vaccine should have several key characteristics, including safety, stability, and the capacity to induce a sufficient and long-lasting immune response with a minimal number of doses. To induce protective immunity against illnesses, different generation vaccines are employed, including attenuated or dead entire organisms (first generation), subunits (second generation), and RNA or DNA vaccines (third generation). To get beyond these obstacles, a reliable vaccination delivery mechanism is needed, one that not only gets the vaccine molecules to the target region where they can trigger long-lasting immune responses but also has few side effects and uses fewer doses. Only a few hundred atoms make up the majority of nanoparticles. Nanoparticles have a relatively significant surface area-to-volume ratio because of their extremely small size. Nanoparticles can have surprising optical, physical, and chemical properties due to this property. Nanotechnology has many benefits for the creation of vaccines for the next generation. A delivery strategy based on nanocarriers can shield vaccines from early deterioration, increase stability, have high adjuvant qualities, and can help with the targeted distribution of an immunogen. The researcher conducts an examination of articles that are in accordance with the issue to be studied. Articles used in the literature review are obtained through the database of international journal providers through PubMed, we investigated clinical studies and discussed what happened in these clinical studies and the extent of the effectiveness of Nanoparticle-Based Vaccines. In order to achieve effective vaccine distribution and generate the required host immunity against infectious diseases, this review article focuses on the applications of nanocarrier-based vaccine formulations and the methodologies utilized for functionalizing nanoparticles.

Keywords: Nanoparticles; Immunogen; Vaccines.

INTRODUCTION

The creation of efficient vaccines is the ultimate objective in the fight against the spread and deadly nature of many of these infectious diseases. Any vaccination that is secure, stable, and able to trigger a robust immune response with a minimal number of doses is desirable. Some alternative vaccine types have demonstrated promising outcomes in their immunogenic profiles, despite the fact that many of the frequently used vaccinations attenuate or kill complete organisms. Some of the top options for innovative vaccinations include subunit vaccines, often known as second-generation vaccines, and third-generation vaccines, which can be RNA- or DNA-based (Doria-Rose et al., 2021; Braz Gomes et al., 2021). Numerous kinds of nanoparticles have innate physical characteristics that can cause an immunological reaction. It has been discovered that cytokine and antibody responses can be induced by gold, carbon, dendrimers, polymers, and liposome nanoparticles. Due to these distinctive properties,

nanoparticles can now be used as adjuvants to boost the immunogenicity of potential vaccines rather than just as vaccine delivery systems. The nanoparticles utilized for this purpose are commonly between 20 and 100 nanometers in size and are also known as nano-immune stimulators or activators (nm). Inorganic NPs like iron and silica, polymeric NPs like chitosan and poly(lactic-co-glycolic) acid (PLGA), cholesterol and lipid liposomes, and VLPs are a few examples of well-known nano-immune stimulators (Bachmann et al., 2010; Bachmann et al., 1993; Baranov et al., 2020).

NPs as drug delivery mechanisms, including antivirals, can inhibit viral reproduction in host cells by releasing antivirals from NPs that block target cell receptors and releasing antivirals from absorbed NPs that are released in a target cell. These main viral replication stages include transcription, replication of phage DNA, synthesis of protein, and assembly. Because of their potential to create prolonged antigen discharge after vaccination injection and to elicit an immune response,

NPs based on organic and inorganic compositions have received extensive research as innovative vaccine approaches. NPs can also create an antigen depot that is controlled and low speed, creating a depot at the injection site that offers the option of antigen preservation over antigen degradation (de Souza et al., 2021; Abo-zeid et al., 2020; Chen and 2020; Chen et al., 2013). When compared to conventional vaccine techniques, nano carrier-based delivery systems have a number of benefits, including as greater adjuvant characteristics, superior stability, and increased protection against premature degradation. Nanocarriers can shield the immunogen from early proteolytic degradation, allowing researchers to investigate

alternative delivery methods when utilized to encapsulate or coat the surface of an antigen. Nanocarriers can enhance the specificity of antigen delivery to APCs and lengthen the time for antigen presentation to these cells and other crucial immune cells essential for long-term immunity in addition to their protective properties. Many different types of nanoparticles, including inorganic and polymeric nanoparticles, virus-like particles (VLPs), liposomes, and self-assembled protein nanoparticles, have been investigated as potential antigen carriers for vaccines. Viral antigens have been effectively delivered using biocompatible inorganic nanoparticles like gold, carbon, and silica (Choi et al., 2021; Chen et al., 2016).

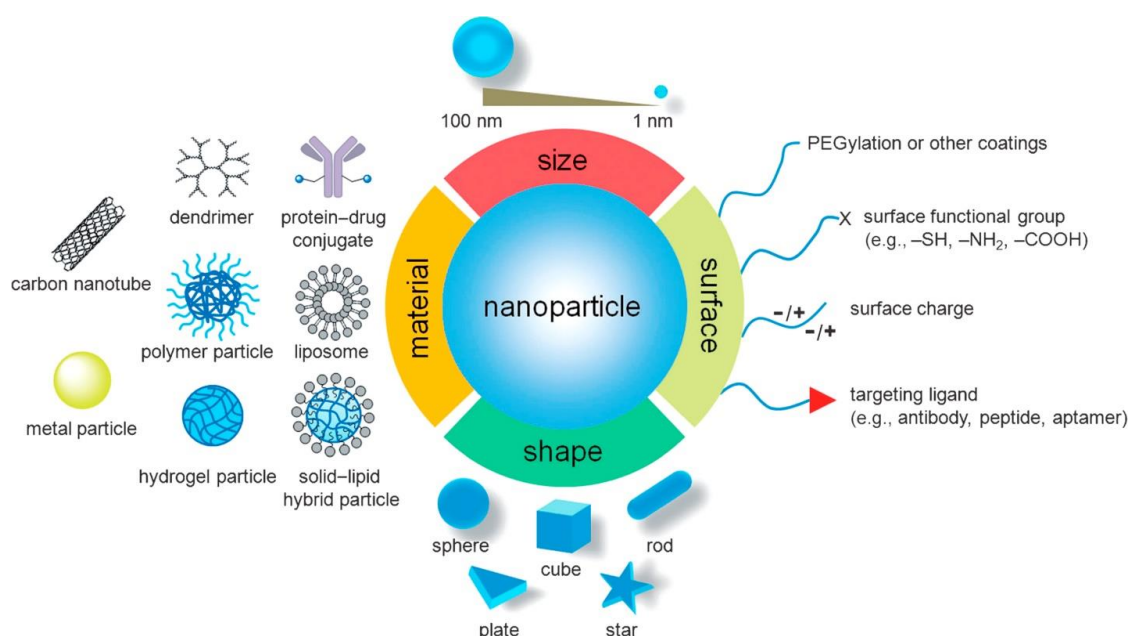


Figure 1. Schematic representation of different types of nanoparticles (NPs) (Heinz et al., 2017).

MATERIALS AND METHODS

Researchers conduct an examination of articles that are in accordance with the issue to be studied. Determination of literature search keywords (search string based on PI (E) COT framework (P=patient/problem; I/E=exposure/implementation; C=control/comparison intervention, O=outcome, T=time) because a good question will help determine the scope of the review and help the strategy of finding the article. Articles used in the literature review are obtained through the database of international journal providers through PubMed, from 2021-2023, Clinical Trials only. The author opens www.PubMed.com. Researchers wrote keywords according to MESH (Medical Subject Heading) namely "Nanoparticle Vaccine" and selected full text. 1. Inclusion Criteria Population or sample is (Nanoparticle-Based Vaccines). 2. Exclusion Criteria

Population or sample other (Nanoparticle-Based Vaccines).

RESULTS AND DISCUSSION

Table 1. (Alimehmeti, 2021), found that severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups. Thomas et al., 2021, found that vaccine efficacy of 86 to 100% was seen across countries and in populations with diverse ages, sexes, races, or ethnic groups, and risk factors for Covid-19 among participants without evidence of previous infection with SARS-CoV-2. Vaccine efficacy against the severe disease was 96.7% (95% CI, 80.3 to

99.9). In South Africa, where the SARS-CoV-2 variant of concern B.1.351 (or beta) was predominant, a vaccine efficacy of 100% (95% CI, 53.5 to 100) was observed. Heath et al., 2021, found that a post hoc analysis showed an efficacy of 86.3% (95% CI, 71.3 to 93.5) against the B.1.1.7 (or alpha) variant and 96.4% (95% CI, 73.8 to 99.5) against non-B.1.1.7 variants. Reactogenicity was generally mild and transient. The incidence of serious adverse events was low and similar in the two groups. Houser et al., 2022, found that Exploratory analyses identified neutralizing antibody responses elicited by the H2HA-Ferritin vaccine in both H2-naive and H2-exposed populations. Furthermore, broadly neutralizing antibody responses against group 1 influenza viruses, including both seasonal H1 and avian H5 subtypes, were induced in the H2-naive population by targeting the HA stem. This ferritin nanoparticle vaccine technology represents a novel, safe and immunogenic platform with potential application for pandemic preparedness and universal influenza vaccine development. Shinde et al., 2021, found that of 41 sequenced isolates, 38 (92.7%) were the B.1.351 variant. Post hoc vaccine efficacy against B.1.351 was 51.0% (95% CI, -0.6 to 76.2) among the HIV-negative participants. Preliminary local and systemic reactogenicity events were more common in the vaccine group; serious adverse events were rare in both groups. Dunkle et al., 2022, found that ten moderate and 4 severe cases occurred, all in placebo recipients, yielding vaccine efficacy against the moderate-to-severe disease of 100% (95% CI, 87.0 to 100). Most sequenced viral genomes (48 of 61, 79%) were variants of concern or interest - largely B.1.1.7 (alpha) (31 of the 35 genomes for variants of concern, 89%). Vaccine efficacy against any variant of concern or interest was 92.6% (95% CI, 83.6 to 96.7). Reactogenicity was mostly mild to moderate and transient but was more frequent among NVX-CoV2373 recipients than among placebo recipients and was more frequent after the second dose than after the first dose. Wei et al., 2022, found that, with a combined endpoint of HBeAg seroconversion, alanine aminotransferase normalization and HBV DNA < 2,000 IU/mL, both 900 µg (18.1%) and 600 µg (14.3%), resulted in significantly higher rate versus placebo (5.0%) ($p = 0.002$ and $p = 0.02$, respectively) at week 76. In stage 2, none (0 of 20) of 900 µg εPA-44-treated patients experienced a serologic relapse. The safety profile of εPA-44 was comparable to that of the placebo. Sahin et al., 2021, found that most participants had a strong response of IFN γ ⁺ or IL-2⁺ CD8⁺ and CD4⁺ T helper type 1 cells, which was detectable throughout the full observation period of nine weeks following the boost. Using peptide-MHC multimer technology, we identified several BNT162b2-induced epitopes that were presented by frequent MHC alleles and conserved in mutant strains. One week after the boost, epitope-specific CD8⁺ T cells of the early-differentiated effector-memory phenotype comprised 0.02-2.92% of total circulating CD8⁺ T cells and were detectable (0.01-0.28%) eight

weeks later. In summary, BNT162b2 elicits an adaptive humoral and poly-specific cellular immune response against epitopes that are conserved in a broad range of variants, at well-tolerated doses. Datoo et al., 2021, found that Participants vaccinated with R21/MM showed high titers of malaria-specific anti-Asn-Ala-Asn-Pro (NANP) antibodies 28 days after the third vaccination, which were almost doubled with the higher adjuvant dose. Titres waned but were boosted to levels similar to peak titers after the primary series of vaccinations after a fourth dose administered 1 year later. Toback et al., 2022, found that No episodes of anaphylaxis or deaths were reported within the substudy. Co-administration resulted in no change to the influenza vaccine immune response although a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. NVX-CoV2373 vaccine efficacy in the substudy (ie, participants aged 18 to <65 years) was 87.5% (95% CI -0.2 to 98.4), and in the main study was 89.8% (95% CI 79.7-95.5). Maruggi et al., 2022, found that High frequencies of spike-specific germinal center B, Th0/Th1 CD4, and CD8 T cell responses were observed in mice. Local tolerance, potential systemic toxicity, and biodistribution of the vaccine were characterized in rats. In hamsters, the vaccine candidate was well-tolerated, markedly reduced viral load in the upper and lower airways, and protected animals against disease in a dose-dependent manner, with no evidence of disease enhancement following the SARS-CoV-2 challenge. Therefore, the SARS-CoV-2 SAM (LNP) vaccine candidate has a favorable safety profile, elicits robust protective immune responses against multiple SARS-CoV-2 variants, and has been advanced to phase 1 clinical evaluation. Madhi et al., 2022, found that, Of the serious adverse events that occurred among HIV-negative people (of whom, two [0.1%] were baseline SARS-CoV-2-negative and four [0.6%] were baseline SARS-CoV-2-positive) and people living with HIV-1 (for whom there were no serious adverse events) in the NVX-CoV2373 group, none were assessed as related to the vaccine. Among participants who were baseline SARS-CoV-2-negative in the NVX-CoV2373 group, the anti-spike IgG geometric mean titers (GMTs) and seroconversion rates (SCRs) were lower in people living with HIV-1 ($n=62$) than in HIV-negative people ($n=1234$) following the first vaccination (GMT: 508.6 vs 1195.3 ELISA units [EU]/mL; SCR: 51.6% vs 81.3%); and similarly so 14 days after the second vaccination for GMTs (14 420.5 vs 31 631.8 EU/mL), whereas the SCR was similar at this point (100.0% vs 99.3%). In the NVX-CoV2373 group, anti-spike IgG GMTs 14 days after the second vaccination were substantially higher in those who were baseline SARS-CoV-2-positive than in those who were baseline SARS-CoV-2-seronegative for HIV-negative participants (100 666.1 vs 31 631.8 EU/mL) and for people living with HIV-1 (98 399.5 vs 14 420.5 EU/mL). This was also the case for angiotensin-converting enzyme 2 receptor-binding antibody and neutralizing antibody

titers. Stuart et al., 2022, found that, Between April 19 and May 14, 2021, 1072 participants were enrolled at a median of 9.4 weeks after receipt of a single dose of ChAd (n=540, 47% female) or BNT (n=532, 40% female). In ChAd-primed participants, geometric mean concentration (GMC) 28 days after a boost of SARS-CoV-2 anti-spike IgG in recipients of ChAd/m1273 (20 114 ELISA laboratory units [ELU]/mL [95% CI 18 160 to 22 279]) and ChAd/NVX (5597 ELU/mL [4756 to 6586]) was non-inferior to that of ChAd/ChAd recipients (1971 ELU/mL [1718 to 2262]) with a GMR of 10.2 (one-sided 98.75% CI 8.4 to ∞) for ChAd/m1273 and 2.8 (2.2 to ∞) for ChAd/NVX, compared with ChAd/ChAd. In BNT-primed participants, non-inferiority was shown for BNT/m1273 (GMC 22 978 ELU/mL [95% CI 20 597 to 25 636]) but not for BNT/NVX (8874 ELU/mL [7391 to 10 654]), compared with BNT/BNT (16 929 ELU/mL [15 025 to 19 075]) with a GMR of 1.3 (one-sided 98.75% CI 1.1 to ∞) for BNT/m1273 and 0.5 (0.4 to ∞) for BNT/NVX, compared with BNT/BNT; however, NVX still induced an 18-fold rise in GMC 28 days after vaccination. There were 15 serious adverse events, none considered related to immunization. Aldrich et al., 2021, found that, As initially tested doses of 5 μ g CV7202 elicited unacceptably high reactogenicity we subsequently tested 1 and 2 μ g doses which were better tolerated. No vaccine-related serious adverse events or withdrawals occurred. Low, dose-dependent VNT responses were detectable from Day 15, and by Day 29%, 31%, and 22% of 1, 2, and 5 μ g groups, respectively, had VNTs \geq 0.5 IU/mL, considered an adequate response by the WHO. After two 1 or 2 μ g doses all recipients had titers \geq 0.5 IU/mL by Day 43. Day 57 GMTs were not significantly lower than those with Rabipur, which elicited adequate responses in all vaccinees after two doses. CV7202-elicited VNT was significantly correlated with RABV-G-specific IgG antibodies ($r^2 = 0.8319$, $p < 0.0001$). Shinde et al., 2022, found that More solicited adverse events were reported by participants in the qNIV group (551 [41.3%] of 1333) than in the IIV4 group (420 [31.8%] of 1319), and were comprised primarily of mild to moderate transient injection site pain (341 [25.6%] in the qNIV group vs 212 [16.1%] in the IIV4 group). Formica et al., 2021, found that, Neutralizing antibody responses exceeded those seen in a panel of convalescent sera for both age groups. Study limitations include the relatively short duration of safety follow-up to date and the current lack of immune persistence data beyond the primary vaccination regimen time point assessments, but these data will accumulate over time. Khobragade et al., 2021, found that The socio-demographic characteristics of the two arms were comparable. About 9.9% of subjects in the recombinant rabies G protein vaccine arm and 17.2% of subjects in the reference arm reported adverse events. The sero-protection on day 14 was found to be 99.24% and 97.72% in the recombinant rabies G protein vaccine

arm and reference vaccine arm respectively and the difference was statistically nonsignificant. August et al., 2021, found that Further evaluation of the potential therapeutic use of mRNA-1944 in clinical trials for the treatment of CHIKV infection is warranted. Shinde et al., 2021, found that, Overall, similar frequencies of solicited and unsolicited adverse events were reported in all treatment groups. Kremsner et al., 2021, found that Responses to 12 μ g were comparable to those observed in convalescent sera from known COVID-19 patients. Mallory et al., 2022, found that 1610 participants were screened from Aug 24, 2020, to Sept 25, 2020. 1282 participants were enrolled, of whom 173 were assigned again to placebo (group A), 106 were re-randomized to NVX-CoV2373-placebo (group B1), and 104 were re-randomized to NVX-CoV2373-NVX-CoV2373 (group B2); after accounting for exclusions and incorrect administration, 172 participants in group A, 102 in group B1, and 105 in group B2 were analysed for safety. Following the active booster, the proportion of participants with available data reporting local (80 [82%] of 97 participants had any adverse event; 13 [13%] had a grade \geq 3 events) and systemic (75 [77%] of 98 participants had any adverse event; 15 [15%] had a grade \geq 3 events) reactions was higher than after primary vaccination (175 [70%] of 250 participants had any local adverse event, 13 [5%] had a grade \geq 3 events; 132 [53%] of 250 had any systemic adverse event, 14 [6%] had a grade \geq 3 events). Local and systemic events were transient in nature (median duration 1.0-2.5 days). In the per-protocol immunogenicity population at day 217 (167 participants in group A, 101 participants in group B1, 101 participants in group B2), IgG geometric mean titers (GMT) had increased by 4.7-fold and MN50 GMT by 4.1-fold for the ancestral SARS-CoV-2 strain compared with the day 35 titers. Heath et al., 2023, found that the Incidence of serious adverse events and adverse events of special interest were similar between groups. Lovell et al., 2022, found that, Neutralizing antibodies levels of the low-dose and high-dose ECV19 groups had FRNT50 geometric mean values of 129 and 316, respectively. Boosting responses and dose responses were observed. Antibodies against the RBD correlated with antibodies against the Spike and with virus neutralization. Gatechompol et al., 2022, found that, an mRNA vaccine expressing a prefusion non-stabilized spike protein is safe and highly immunogenic. Masuda et al., 2022, found that, Between 12 February 2021 and 17 March 2021, 326 subjects were screened, and 200 participants enrolled and randomized: NVX-CoV2373, n = 150; placebo, n = 50. Solicited adverse events (AEs) through 7 days after each injection occurred in 121/150 (80.7%) and 11/50 (22.0%) participants in the NVX-CoV2373 and placebo arms, respectively. In the NVX-CoV2373 arm, tenderness and injection site pain were the most frequently reported solicited AEs after each vaccination, irrespective of age. Robust immune responses occurred with NVX-CoV2373

(n = 150) by day 36: IgG geometric mean fold rise (95% confidence interval) 259 (219, 306); seroconversion rate 100% (97.6, 100). No such response occurred with a placebo (n = 49). Ishikawa et al., 2021, found that The most common adverse event (AE) was injection site skin reaction (86.7%). No grade 3 or higher drug-related AEs were observed. No tumor responses were observed, and three patients (30%) had stable disease. The immune response was comparable between the two cohorts, and all patients (100%) achieved antibody responses with a median of 2.5 vaccinations. Comparing CHP-NY-ESO-1 alone to the poly-ICLC combination, all patients in both groups exhibited antibody responses, but the titers were higher in the combination group. In a mouse model, adding an anti-PD-1 antibody to the combination of CHP-NY-ESO-1/poly-ICLC suppressed the growth of

NY-ESO-1-expressing tumors. Combining the vaccine with PD-1 blockade holds promise in human trials. Li et al., 2022, found that, In younger participants, neutralizing antibody (nAb) geometric mean titers (GMTs) for the 10 and 30 µg dose levels declined from 233 and 254 (21 days after dose 2) to 55 and 87 at month 3, respectively, and to 16 and 27 at month 6, respectively. In older participants, nAb GMTs declined from 80 and 160 (21 days after dose 2) to 10 and 21 at month 6. Overall, higher antibody titers were observed in younger participants, and the 30 µg dose induced higher levels of nAb, which declined more slowly by month 6. No serious adverse events were reported in the vaccine group. Wei et al., 2021, found that EpNP, carrying the neutralizing epitope Hla121-138, is a good candidate for a vaccine against SA.

Table 1. Clinical studies using Nanotechnology-Based Vaccines.

Authors	Title	Date and Type of the Study	Method	Results
Alimehmeti	Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine	Clinical Trial 2021	This phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States. Persons at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 µg) or a placebo 28 days apart. The primary endpoint was the prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2.	Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups.
Thomas et al.	Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months	Randomized Controlled Trial 2021	In an ongoing, placebo-controlled, observer-blinded, multinational, pivotal efficacy trial, we randomly assigned 44,165 participants 16 years of age or older and 2264 participants 12 to 15 years of age to receive two 30-µg doses, at 21 days apart, of BNT162b2 or placebo. The trial endpoints were vaccine efficacy against laboratory-confirmed Covid-19 and safety, which were both evaluated 6 months after vaccination.	Vaccine efficacy of 86 to 100% was seen across countries and in populations with diverse ages, sexes, races, or ethnic groups, and risk factors for Covid-19 among participants without evidence of previous infection with SARS-CoV-2. Vaccine efficacy against the severe disease was 96.7% (95% CI, 80.3 to 99.9). In South Africa, where the SARS-CoV-2 variant of concern B.1.351 (or beta) was predominant, a vaccine efficacy of 100% (95% CI, 53.5 to 100) was observed.

Table 1. Cont.

Authors	Title	Date and Type of the Study	Method	Results
Heath et al.	Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine	Clinical Trial 2021	In this phase 3, randomized, observer-blinded, placebo-controlled trial conducted at 33 sites in the United Kingdom, we assigned adults between the ages of 18 and 84 years in a 1:1 ratio to receive two intramuscular 5- μ g doses of NVX-CoV2373 or placebo administered 21 days apart. The primary efficacy endpoint was virologically confirmed mild, moderate, or severe SARS-CoV-2 infection with an onset at least 7 days after the second injection in participants who were serologically negative at baseline.	A post hoc analysis showed an efficacy of 86.3% (95% CI, 71.3 to 93.5) against the B.1.1.7 (or alpha) variant and 96.4% (95% CI, 73.8 to 99.5) against non-B.1.1.7 variants. Reactogenicity was generally mild and transient. The incidence of serious adverse events was low and similar in the two groups.
Houser et al.	Safety and immunogenicity of a ferritin nanoparticle H2 influenza vaccine in healthy adults: a phase I trial	Clinical Trial 2022	Conducted a first-in-human, randomized, open-label, phase I clinical trial (NCT03186781) to evaluate a novel ferritin (H2HA-Ferritin) nanoparticle influenza vaccine platform. The H2 subtype has not circulated in humans since 1968. Adults born after 1968 have been exposed to only the H1 subtype of group 1 influenza viruses, which shares a conserved stem with H2. Including both H2-naive and H2-exposed adults in the trial allowed us to evaluate memory responses against the conserved stem domain in the presence or absence of pre-existing responses against the immunodominant HA head domain.	Exploratory analyses identified neutralizing antibody responses elicited by the H2HA-Ferritin vaccine in both H2-naive and H2-exposed populations. Furthermore, broadly neutralizing antibody responses against group 1 influenza viruses, including both seasonal H1 and avian H5 subtypes, were induced in the H2-naive population by targeting the HA stem. This ferritin nanoparticle vaccine technology represents a novel, safe and immunogenic platform with potential application for pandemic preparedness and universal influenza vaccine development.
Shinde et al.	Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant	Clinical Trial 2021	In this phase 2a-b trial in South Africa, we randomly assigned human immunodeficiency virus (HIV)-negative adults between the ages of 18 and 84 years or medically stable HIV-positive participants between the ages of 18 and 64 years in a 1:1 ratio to receive two doses of either the NVX-CoV2373 vaccine (5 μ g of recombinant spike protein with 50 μ g of Matrix-M1 adjuvant) or placebo. The primary endpoints were safety and vaccine efficacy against laboratory-confirmed symptomatic Covid-19 at 7 days or more after the second dose among participants without previous SARS-CoV-2 infection.	Of 41 sequenced isolates, 38 (92.7%) were the B.1.351 variant. Post hoc vaccine efficacy against B.1.351 was 51.0% (95% CI, -0.6 to 76.2) among the HIV-negative participants. Preliminary local and systemic reactogenicity events were more common in the vaccine group; serious adverse events were rare in both groups.
Dunkle et al.	Efficacy and Safety of NVX-CoV2373 in Adults in the United	Clinical Trial 2022	conducted a phase 3, randomized, observer-blinded, placebo-controlled trial in the	Ten moderate and 4 severe cases occurred, all in placebo recipients, yielding vaccine efficacy against the

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	States and Mexico		United States and Mexico during the first half of 2021 to evaluate the efficacy and safety of NVX-CoV2373 in adults (≥ 18 years of age) who had not had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Participants were randomly assigned in a 2:1 ratio to receive two doses of NVX-CoV2373 or placebo 21 days apart. The primary objective was to determine vaccine efficacy against reverse-transcriptase-polymerase-chain-reaction-confirmed Covid-19 occurring at least 7 days after the second dose. Vaccine efficacy against moderate-to-severe disease and against different variants was also assessed.	moderate-to-severe disease of 100% (95% CI, 87.0 to 100). Most sequenced viral genomes (48 of 61, 79%) were variants of concern or interest - largely B.1.1.7 (alpha) (31 of the 35 genomes for variants of concern, 89%). Vaccine efficacy against any variant of concern or interest was 92.6% (95% CI, 83.6 to 96.7). Reactogenicity was mostly mild to moderate and transient but was more frequent among NVX-CoV2373 recipients than among placebo recipients and was more frequent after the second dose than after the first dose.
Wei et al.	Efficacy and safety of a nanoparticle therapeutic vaccine in patients with chronic hepatitis B: A randomized clinical trial	Clinical Trial 2022	A two-stage phase 2 trial, which included a 76-week, randomized, double-blind, placebo-controlled trial (stage 1) and a 68-week open-label extension (stage 2), was conducted in 15 centers across China.	With a combined endpoint of HBeAg seroconversion, alanine aminotransferase normalization and HBV DNA $< 2,000$ IU/mL, both 900 μg (18.1%) and 600 μg (14.3%), resulted in significantly higher rate versus placebo (5.0%) ($p = 0.002$ and $p = 0.02$, respectively) at week 76. In stage 2, none (0 of 20) of 900 μg ePA-44-treated patients experienced a serologic relapse. The safety profile of ePA-44 was comparable to that of the placebo.
Sahin et al.	BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans	Clinical Trial 2021	extend a previous phase-I/II trial report2 by presenting data on the immune response induced by BNT162b2 prime-boost vaccination from an additional phase-I/II trial in healthy adults (18-55 years old).	Most participants had a strong response of IFN γ + or IL-2+ CD8+ and CD4+ T helper type 1 cell, which was detectable throughout the full observation period of nine weeks following the boost. Using peptide-MHC multimer technology, we identified several BNT162b2-induced epitopes that were presented by frequent MHC alleles and conserved in mutant strains. One week after the boost, epitope-specific CD8+ T cells of the early-differentiated effector-memory phenotype comprised 0.02-2.92% of total circulating CD8+ T cells and were detectable (0.01-0.28%) eight weeks later. In summary, BNT162b2 elicits an adaptive humoral and poly-specific cellular immune response against epitopes that are conserved in a broad range of variants, at well-tolerated doses.
Datoo et al.	Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised	Clinical Trial 2021	In this double-blind, randomized, controlled, phase 2b trial, the low-dose circumsporozoite protein-based vaccine R21, with two different doses of adjuvant Matrix-M (MM), was given to children aged 5-17 months in Nanoro,	Participants vaccinated with R21/MM showed high titres of malaria-specific anti-Asn-Ala-Asn-Pro (NANP) antibodies 28 days after the third vaccination, which were almost doubled with the higher adjuvant dose. Titres waned but were boosted to levels similar to peak titres after the

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	controlled trial		Burkina Faso-a highly seasonal malaria transmission setting. Three vaccinations were administered at 4-week intervals before the malaria season, with a fourth dose 1 year later. All vaccines were administered intramuscularly into the thigh. Group 1 received 5 µg R21 plus 25 µg MM, group 2 received 5 µg R21 plus 50 µg MM, and group 3, the control group, received rabies vaccinations. Children were randomly assigned (1:1:1) to groups 1-3. An independent statistician generated a random allocation list, using block randomisation with variable block sizes, which was used to assign participants. Participants, their families, and the local study team were all masked to group allocation. Only the pharmacists preparing the vaccine were unmasked to group allocation. Vaccine safety, immunogenicity, and efficacy were evaluated over 1 year. The primary objective assessed the protective efficacy of R21 plus MM (R21/MM) from 14 days after the third vaccination to 6 months. Primary analyses of vaccine efficacy were based on a modified intention-to-treat population, which included all participants who received three vaccinations, allowing for the inclusion of participants who received the wrong vaccine at any time point.	primary series of vaccinations after a fourth dose administered 1 year later.
Toback et al.	Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomized, observer-blinded, placebo-controlled, phase 3 trial	Clinical Trial 2022	a planned exploratory substudy as part of the randomized, observer-blinded, placebo-controlled, phase 3 trial of the safety and efficacy of the COVID-19 vaccine (NVX-CoV2373) by co-administering the influenza vaccine at four study hospitals in the UK. Approximately, the first 400 participants meeting the main study entry criteria-with no contraindications to influenza vaccination-were invited to join the substudy. Participants of the main study were randomly assigned (1:1) to receive two intramuscular injections of either NVX-CoV2373 (5 µg) or placebo (normal saline) 21 days apart; participants enrolled into the substudy were co-vaccinated with a single (0.5 mL)	No episodes of anaphylaxis or deaths were reported within the substudy. Co-administration resulted in no change to influenza vaccine immune response although a reduction in antibody responses to the NVX-CoV2373 vaccine was noted. NVX-CoV2373 vaccine efficacy in the substudy (ie, participants aged 18 to <65 years) was 87.5% (95% CI -0.2 to 98.4) and in the main study was 89.8% (95% CI 79.7-95.5).

Authors	Title	Date and Type of the Study	Method	Results
			<p>intramuscular, age-appropriate (quadrivalent influenza cell-based vaccine [Flucelvax Quadrivalent; Seqirus UK, Maidenhead] for those aged 18-64 years and adjuvanted trivalent influenza vaccine [Fluad; Seqirus UK, Maidenhead] for those ≥ 65 years), licensed, influenza vaccine on the opposite deltoid to that of the first study vaccine dose or placebo. The influenza vaccine was administered in an open-label manner and at the same time as the first study injection. Reactogenicity was evaluated via an electronic diary for 7 days after vaccination in addition to monitoring for unsolicited adverse events, medically attended adverse events and serious adverse events. Immunogenicity was assessed with influenza haemagglutination inhibition and SARS-CoV-2 anti-spike protein IgG assays. Vaccine efficacy against PCR-confirmed, symptomatic COVID-19 was assessed in participants who were seronegative at baseline, received both doses of the study vaccine or placebo, had no major protocol deviations affecting the primary endpoint, and had no confirmed cases of symptomatic COVID-19 from the first dose until 6 days after the second dose (per-protocol efficacy population). Immunogenicity was assessed in participants who received scheduled two doses of the study vaccine, had a baseline sample and at least one post-vaccination sample, and had no major protocol violations before unmasking (per-protocol immunogenicity population). Reactogenicity was analyzed in all participants who received at least one dose of NVX-CoV2373 or placebo and had data collected for reactogenicity events. Safety was analyzed in all participants who received at least one dose of NVX-CoV2373 or placebo. Comparisons were made between participants of the sub-study and the main study (who were not co-vaccinated for influenza).</p>	

Authors	Title	Date and Type of the Study	Method	Results
Maruggi et al.	A self-amplifying mRNA SARS-CoV-2 vaccine candidate induces safe and robust protective immunity in preclinical models	Clinical Trial 2022	Assessed immunogenicity and, for the first time, toxicity, biodistribution, and protective efficacy in preclinical models of a two-dose self-amplifying messenger RNA (SAM) vaccine, encoding a prefusion-stabilized spike antigen of SARS-CoV-2 Wuhan-Hu-1 strain and delivered by lipid nanoparticles (LNPs). In mice, one immunization with the SAM vaccine elicited a robust spike-specific antibody response, which was further boosted by a second immunization, and effectively neutralized the matched SARS-CoV-2 Wuhan strain as well as B.1.1.7 (Alpha), B.1.351 (Beta) and B.1.617.2 (Delta) variants.	High frequencies of spike-specific germinal center B, Th0/Th1 CD4, and CD8 T cell responses were observed in mice. Local tolerance, potential systemic toxicity, and biodistribution of the vaccine were characterized in rats. In hamsters, the vaccine candidate was well-tolerated, markedly reduced viral load in the upper and lower airways, and protected animals against disease in a dose-dependent manner, with no evidence of disease enhancement following the SARS-CoV-2 challenge. Therefore, the SARS-CoV-2 SAM (LNP) vaccine candidate has a favorable safety profile, elicits robust protective immune responses against multiple SARS-CoV-2 variants, and has been advanced to phase 1 clinical evaluation
Madhi et al.	Immunogenicity and safety of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine in people living with and without HIV-1 infection: a randomized, controlled, phase 2A/2B trial	Clinical Trial 2022	In this randomized, observer-blinded, multicentre, placebo-controlled phase 2A/B trial in South Africa, participants aged 18-84 years, with and without underlying HIV-1, were enrolled from 16 sites and randomly assigned (1:1) to receive two intramuscular injections of NVX-CoV2373 or placebo, 21 days apart. People living with HIV-1 were on stable antiretroviral therapy and had an HIV-1 viral load of few than 1000 copies per mL. Vaccine dosage was 5 µg SARS-CoV-2 recombinant spike protein with 50 µg Matrix-M adjuvant, whereas 0.9% saline was used as a placebo injection (volume 0.5 mL each). All study staff and participants remained masked to study group assignment. We previously reported an interim analysis on the efficacy and safety of the NVX-CoV2373 vaccine (coprimary endpoints). In this article, we present an expanded safety analysis for the full cohort of participants and report on the secondary objective of vaccine immunogenicity in the full cohort of people living with HIV-1 and in HIV-negative individuals overall and stratified by baseline SARS-CoV-2 serostatus.	Of the serious adverse events that occurred among HIV-negative people (of whom, two [0.1%] were baseline SARS-CoV-2-negative and four [0.6%] were baseline SARS-CoV-2-positive) and people living with HIV-1 (for whom there were no serious adverse events) in the NVX-CoV2373 group, none were assessed as related to the vaccine. Among participants who were baseline SARS-CoV-2-negative in the NVX-CoV2373 group, the anti-spike IgG geometric mean titres (GMTs) and seroconversion rates (SCRs) were lower in people living with HIV-1 (n=62) than in HIV-negative people (n=1234) following the first vaccination (GMT: 508.6 vs 1195.3 ELISA units [EU]/mL; SCR: 51.6% vs 81.3%); and similarly so 14 days after the second vaccination for GMTs (14 420.5 vs 31 631.8 EU/mL), whereas the SCR was similar at this point (100.0% vs 99.3%). In the NVX-CoV2373 group, anti-spike IgG GMTs 14 days after the second vaccination were substantially higher in those who were baseline SARS-CoV-2-positive than in those who were baseline SARS-CoV-2-seronegative for HIV-negative participants (100 666.1 vs 31 631.8 EU/mL) and for people living with HIV-1 (98 399.5 vs 14 420.5 EU/mL). This was also the case for angiotensin-converting enzyme 2 receptor-binding antibodies and neutralizing antibody-titers.
Stuart et al.	Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary	Clinical Trial 2022	Com-COV2 is a single-blind, randomized, non-inferiority trial in which adults aged 50 years and older, previously immunised with a single dose of ChAd or	Between April 19 and May 14, 2021, 1072 participants were enrolled at a median of 9.4 weeks after receipt of a single dose of ChAd (n=540, 47% female) or BNT (n=532, 40% female).

Authors	Title	Date and Type of the Study	Method	Results
	vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial		BNT in the community, were randomly assigned (in random blocks of three and six) within these cohorts in a 1:1:1 ratio to receive a second dose intramuscularly (8-12 weeks after the first dose) with the homologous vaccine, m1273, or NVX. The primary endpoint was the geometric mean ratio (GMR) of serum SARS-CoV-2 anti-spike IgG concentrations measured by ELISA in heterologous versus homologous schedules at 28 days after the second dose, with a non-inferiority criterion of the GMR above 0.63 for the one-sided 98.75% CI. The primary analysis was on the per-protocol population, who were seronegative at baseline. Safety analyses were done for all participants who received a dose of the study vaccine.	In ChAd-primed participants, geometric mean concentration (GMC) 28 days after a boost of SARS-CoV-2 anti-spike IgG in recipients of ChAd/m1273 (20 114 ELISA laboratory units [ELU]/mL [95% CI 18 160 to 22 279]) and ChAd/NVX (5597 ELU/mL [4756 to 6586]) was non-inferior to that of ChAd/ChAd recipients (1971 ELU/mL [1718 to 2262]) with a GMR of 10.2 (one-sided 98.75% CI 8.4 to ∞) for ChAd/m1273 and 2.8 (2.2 to ∞) for ChAd/NVX, compared with ChAd/ChAd. In BNT-primed participants, non-inferiority was shown for BNT/m1273 (GMC 22 978 ELU/mL [95% CI 20 597 to 25 636]) but not for BNT/NVX (8874 ELU/mL [7391 to 10 654]), compared with BNT/BNT (16 929 ELU/mL [15 025 to 19 075]) with a GMR of 1.3 (one-sided 98.75% CI 1.1 to ∞) for BNT/m1273 and 0.5 (0.4 to ∞) for BNT/NVX, compared with BNT/BNT; however, NVX still induced an 18-fold rise in GMC 28 days after vaccination. There were 15 serious adverse events, none considered related to immunization.
Aldrich et al.	Proof-of-concept of a low-dose unmodified mRNA-based rabies vaccine formulated with lipid nanoparticles in human volunteers: A phase 1 trial	Clinical Trial 2021	In this phase 1, multi-center, controlled study in Belgium and Germany we enrolled 55 healthy 18-40-year-olds to receive intramuscular injections of 5 μ g (n = 10), 1 μ g (n = 16), or 2 μ g (n = 16) CV7202 on Day 1; subsets (n = 8) of 1 μ g and 2 μ g groups received second doses on Day 29. Controls (n = 10) received the rabies vaccine, Rabipur, on Days 1, 8, and 29. Safety and reactogenicity were assessed up to 28 days post-vaccination using diary cards; immunogenicity was measured as RABV-G-specific neutralizing titers (VNT) by RFFIT and IgG by ELISA.	As initially tested doses of 5 μ g CV7202 elicited unacceptably high reactogenicity we subsequently tested 1 and 2 μ g doses which were better tolerated. No vaccine-related serious adverse events or withdrawals occurred. Low, dose-dependent VNT responses were detectable from Day 15, and by Day 29%, 31%, and 22% of 1, 2 and 5 μ g groups, respectively, had VNTs \geq 0.5 IU/mL, considered an adequate response by the WHO. After two 1 or 2 μ g doses all recipients had titers \geq 0.5 IU/mL by Day 43. Day 57 GMTs were not significantly lower than those with Rabipur, which elicited adequate responses in all vaccinees after two doses. CV7202-elicited VNT was significantly correlated with RABV-G-specific IgG antibodies ($r^2 = 0.8319$, $p < 0.0001$).
Shinde et al.	Comparison of the safety and immunogenicity of a novel Matrix-M-adjuvanted nanoparticle influenza vaccine with a quadrivalent seasonal influenza vaccine in older adults: a phase 3 randomized controlled trial	Clinical Trial 2022	This was phase 3 randomized, observer-blinded, active-comparator controlled trial done across 19 US community-based clinical research sites during the 2019-20 influenza season. Participants were clinically stable and community-dwelling, aged at least 65 years and were randomised in a 1:1 ratio using an interactive web response system to receive a single intramuscular dose of qNIV or IIV4. The primary objective was	More solicited adverse events were reported by participants in the qNIV group (551 [41.3%] of 1333) than in the IIV4 group (420 [31.8%] of 1319), and were comprised primarily of mild to moderate transient injection site pain (341 [25.6%] in the qNIV group vs 212 [16.1%] in the IIV4 group).

Authors	Title	Date and Type of the Study	Method	Results
			to describe the safety and show that qNIV was immunologically non-inferior to IIV4. The primary outcomes were adverse events by treatment group and comparative haemagglutination-inhibiting antibody responses (assayed with egg-propagated virus) on day 28, summarised in terms of the ratio of geometric mean titres (GMTRqNIV/IIV4) and seroconversion rate (SCR) difference between participants receiving qNIV or IIV4 for all four vaccine homologous influenza strains. The immunogenicity outcome was measured in the per-protocol population. Non-inferiority was shown if the lower bound of the two-sided 95% CI on the GMTRqNIV/IIV4 was at least 0.67 and the lower bound of the two-sided 95% CI on the SCR difference -was at least -10%.	
Formica et al.	Different dose regimens of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373) in younger and older adults: A phase 2 randomized placebo-controlled trial	Clinical Trial 2021	The phase 2 component of our randomized, placebo-controlled, phase 1 to 2 trial was designed to identify which dosing regimen of NVX-CoV2373 should move forward into late-phase studies and was based on immunogenicity and safety data through Day 35 (14 days after the second dose). The trial was conducted at 9 sites in Australia and 8 sites in the United States. Participants in 2 age groups (aged 18 to 59 and 60 to 84 years) were randomly assigned to receive either 1 or 2 intramuscular doses of 5- μ g or 25- μ g NVX-CoV2373 or placebo, 21 days apart. Primary endpoints were immunoglobulin G (IgG) anti-spike protein response, 7-day solicited reactogenicity and unsolicited adverse events. A key secondary endpoint was a wild-type virus-neutralizing antibody response. After enrollment, 1,288 participants were randomly assigned to 1 of 4 vaccine groups or placebo, with 1,283 participants administered at least 1 study treatment.	Neutralizing antibody responses exceeded those seen in a panel of convalescent sera for both age groups. Study limitations include the relatively short duration of safety follow-up to date and the current lack of immune persistence data beyond the primary vaccination regimen time point assessments, but these data will accumulate over time.
Khobragade et al.	Safety and Immunogenicity of a novel three-dose recombinant nanoparticle rabies G protein vaccine administered as	Clinical Trial 2021	A multi-centric, open-label, assessor-blind, center-specific block randomized, parallel design, phase III clinical study was conducted among 800 subjects. The eligible subjects were randomized in a 2:1 ratio	The socio-demographic characteristics of the two arms were comparable. About 9.9% of subjects in the recombinant rabies G protein vaccine arm and 17.2% of subjects in the reference arm reported adverse events. The seroprotection on day 14 was

Authors	Title	Date and Type of the Study	Method	Results
	simulated post-exposure immunization: A randomized, comparator-controlled, multicenter, phase III clinical study		for the recombinant rabies G protein vaccine and the reference vaccine. Subjects in the recombinant rabies G protein vaccine arm received three doses of vaccine on days 0, 3, and 7, while subjects in the reference vaccine arm received five doses of WHO-prequalified vaccine on days 0, 3, 7, 14, and 28.	found to be 99.24% and 97.72% in the recombinant rabies G protein vaccine arm and reference vaccine arm respectively and the difference was statistically nonsignificant.
August et al.	A phase 1 trial of lipid-encapsulated mRNA encoding a monoclonal antibody with neutralizing activity against Chikungunya virus	Clinical Trial 2021	This phase 1, first-in-human, randomized, placebo-controlled, proof-of-concept trial conducted from January 2019 to June 2020 evaluated the safety and pharmacology of mRNA-1944, a lipid nanoparticle-encapsulated messenger RNA encoding the heavy and light chains of a CHIKV-specific monoclonal neutralizing antibody, CHKV-24	Further evaluation of the potential therapeutic use of mRNA-1944 in clinical trials for the treatment of CHIKV infection is warranted.
Shinde et al.	Induction of Cross-Reactive Hemagglutination Inhibiting Antibody and Polyfunctional CD4+ T-Cell Responses by a Recombinant Matrix-M-Adjuvanted Hemagglutinin Nanoparticle Influenza Vaccine	Randomized Controlled Trial 2021	A randomized, observer-blind, comparator-controlled (trivalent high-dose inactivated influenza vaccine [IIV3-HD] or quadrivalent recombinant influenza vaccine [RIV4]), safety and immunogenicity trial of qNIV (5 doses/formulations) in healthy adults ≥ 65 years. Vaccine immunogenicity was measured by hemagglutination-inhibition assays using reagents that express wild-type hemagglutination inhibition (wt-HAI) sequences and cell-mediated immune responses.	Overall, similar frequencies of solicited and unsolicited adverse events were reported in all treatment groups.
Kremsner et al.	Safety and immunogenicity of an mRNA-lipid nanoparticle vaccine candidate against SARS-CoV-2 : A phase 1 randomized clinical trial	Clinical Trial 2021	This is an interim analysis of a dosage escalation phase 1 study in healthy 18-60-year-old volunteers in Hannover, Munich, and Tübingen, Germany, and Ghent, Belgium. After giving 2 intramuscular doses of CVnCoV or placebo 28 days apart we assessed solicited local and systemic adverse events (AE) for 7 days and unsolicited AEs for 28 days after each vaccination. Immunogenicity was measured as enzyme-linked immunosorbent assay (ELISA) IgG antibodies to SARS-CoV-2 S-protein and receptor binding domain (RBD), and SARS-CoV-2 neutralizing titers (MN50).	Responses to 12 μ g were comparable to those observed in convalescent sera from known COVID-19 patients.
Mallory et al.	Safety and immunogenicity following a homologous booster dose of a SARS-CoV-2 recombinant	Clinical Trial 2022	This secondary analysis of phase 2, randomised study assessed a single booster dose of a SARS-CoV-2 recombinant spike protein vaccine with Matrix-M adjuvant (NVX-CoV2373) in	1610 participants were screened from Aug 24, 2020, to Sept 25, 2020. 1282 participants were enrolled, of whom 173 were assigned again to placebo (group A), 106 were re-randomized to NVX-CoV2373-placebo (group B1),

Authors	Title	Date and Type of the Study	Method	Results
	spike protein vaccine (NVX-CoV2373): a secondary analysis of a randomised, placebo-controlled, phase 2 trial		healthy adults aged 18-84 years, recruited from 17 clinical centres in the USA and Australia.	and 104 were re-randomized to NVX-CoV2373-NVX-CoV2373 (group B2); after accounting for exclusions and incorrect administration, 172 participants in group A, 102 in group B1, and 105 in group B2 were analyzed for safety. Following the active booster, the proportion of participants with available data reporting local (80 [82%] of 97 participants had any adverse event; 13 [13%] had a grade ≥ 3 events) and systemic (75 [77%] of 98 participants had any adverse event; 15 [15%] had a grade ≥ 3 events) reactions was higher than after primary vaccination (175 [70%] of 250 participants had any local adverse event, 13 [5%] had a grade ≥ 3 events; 132 [53%] of 250 had any systemic adverse event, 14 [6%] had a grade ≥ 3 events). Local and systemic events were transient in nature (median duration 1.0-2.5 days). In the per-protocol immunogenicity population at day 217 (167 participants in group A, 101 participants in group B1, 101 participants in group B2), IgG geometric mean titers (GMT) had increased by 4.7-fold and MN50 GMT by 4.1-fold for the ancestral SARS-CoV-2 strain compared with the day 35 titers.
Heath et al.	Safety and Efficacy of the NVX-CoV2373 Coronavirus Disease 2019 Vaccine at Completion of the Placebo-Controlled Phase of a Randomized Controlled Trial	Clinical Trial 2023	Adults aged 18-84 years received 2 doses of NVX-CoV2373 or placebo (1:1) and were monitored for virologically confirmed mild, moderate, or severe COVID-19 (onset from 7 days after second vaccination). Participants who developed immunoglobulin G (IgG) against nucleocapsid protein but did not show symptomatic COVID-19 were considered asymptomatic. Secondary outcomes included anti-spike (S) IgG responses, wild-type virus neutralization, and T-cell responses.	Incidence of serious adverse events and adverse events of special interest were similar between groups.
Lovell et al.	Interim analysis from a phase 2 randomized trial of EuCorVac-19: a recombinant protein SARS-CoV-2 RBD nanoliposome vaccine	Clinical Trial 2022	An initial study of phase 2 randomized, observer-blind, placebo-controlled trial to assess the immunogenicity, safety, and tolerance of ECV19 was carried out between July and October 2021. Two hundred twenty-nine participants were enrolled at 5 hospital sites in South Korea. Healthy adults aged 19-75 without prior known exposure to COVID-19 were vaccinated intramuscularly on day 0 and day 21. Of the participants who received two vaccine doses according to protocol, 100	Neutralizing antibody levels of the low-dose and high-dose ECV19 groups had FRNT50 geometric mean values of 129 and 316, respectively. Boosting responses and dose responses were observed. Antibodies against the RBD correlated with antibodies against the Spike and with virus neutralization.

Authors	Title	Date and Type of the Study	Method	Results
			received high-dose ECV19 (20 µg RBD), 96 received low-dose ECV19 (10 µg RBD), and 27 received a placebo. Local and systemic adverse events were monitored. Serum was assessed on days 0, 21, and 42 for immunogenicity analysis by ELISA and neutralizing antibody response by focus reduction neutralization test (FRNT).	
Gatechompol et al.	Safety and immunogenicity of a prefusion non-stabilized spike protein mRNA COVID-19 vaccine: a phase I trial	Clinical Trial 2022	Seventy-two eligible volunteers, 36 of whom were aged 18-55 (adults) and 36 aged 56-75 (elderly), were enrolled. Two doses of vaccine were administered 21 d apart at 10, 25 or 50 µg per dose (12 per group). The primary outcome was safety, and the secondary outcome was immunogenicity. All three dosages of ChulaCov19 were well tolerated and elicited robust dose-dependent and age-dependent B- and T-cell responses	mRNA vaccine expressing a prefusion non-stabilized spike protein is safe and highly immunogenic.
Masuda et al.	Safety and immunogenicity of NVX-CoV2373 (TAK-019) vaccine in healthy Japanese adults: Interim report of a phase I/II randomized controlled trial	Clinical Trial 2022	This phase 1/2, randomized, observer-blind, placebo-controlled trial conducted in Japan (two sites), enrolled healthy Japanese adults aged ≥ 20 years with no history/risk of SARS-CoV-2 infection and no prior exposure to other approved/investigational SARS-CoV-2 vaccines or treatments. Participants were stratified by age (< 65 or ≥ 65 years) and randomized to receive two doses of either NVX-CoV2373 (5 µg SARS-CoV-2 rS; 50 µg Matrix-M1) or placebo, 21 days apart. Primary outcomes were safety and immunogenicity assessed by serum IgG antibody levels against SARS-CoV-2 rS protein on day 36. Herein, we report the primary data analysis at 4 weeks after the second dose, ahead of the 12-month follow-up completion (data cut-off: 8 May 2021).	Between 12 February 2021 and 17 March 2021, 326 subjects were screened, and 200 participants were enrolled and randomized: NVX-CoV2373, n = 150; placebo, n = 50. Solicited adverse events (AEs) through 7 days after each injection occurred in 121/150 (80.7%) and 11/50 (22.0%) participants in the NVX-CoV2373 and placebo arms, respectively. In the NVX-CoV2373 arm, tenderness and injection site pain were the most frequently reported solicited AEs after each vaccination, irrespective of age. Robust immune responses occurred with NVX-CoV2373 (n = 150) by day 36: IgG geometric mean fold rise (95% confidence interval) 259 (219, 306); seroconversion rate 100% (97.6, 100). No such response occurred with a placebo (n = 49).
Ishikawa et al.	Safety and antibody immune response of CHP-NY-ESO-1 vaccine combined with poly-ICLC in advanced or recurrent esophageal cancer patients	Clinical Trial 2021	Conducted a phase 1 clinical trial of CHP-NY-ESO-1 with poly-ICLC in patients with advanced or recurrent esophageal cancer. CHP-NY-ESO-1/poly-ICLC (µg/mg) was administered at a dose of 200/0.5 or 200/1.0 (cohorts 1 and 2, respectively) every 2 weeks for a total of six doses. The primary endpoints were	The most common adverse event (AE) was injection site skin reaction (86.7%). No grade 3 or higher drug-related AEs were observed. No tumor responses were observed, and three patients (30%) had stable disease. The immune response was comparable between the two cohorts, and all patients (100%) achieved antibody responses with a median of 2.5 vaccinations. Comparing CHP-NY-

Authors	Title	Date and Type of the Study	Method	Results
			safety and immune response. The secondary endpoint was tumor response. In total, 16 patients were enrolled, and six patients in each cohort completed the trial.	ESO-1 alone to the poly-ICLC combination, all patients in both groups exhibited antibody responses, but the titers were higher in the combination group. In a mouse model, adding an anti-PD-1 antibody to the combination of CHP-NY-ESO-1/poly-ICLC suppressed the growth of NY-ESO-1-expressing tumors. Combining the vaccine with PD-1 blockade holds promise in human trials.
Li et al.	Immune Persistence and Safety After SARS-CoV-2 BNT162b1 mRNA Vaccination in Chinese Adults: A Randomized, Placebo-Controlled, Double-Blind Phase 1 Trial	Clinical Trial 2022	Immune persistence was determined at month 3 in 72 younger participants (aged 18-55 years) and at month 6 in 70 younger and 69 older participants (aged 65-85 years).	In younger participants, neutralizing antibody (nAb) geometric mean titers (GMTs) for the 10 and 30 µg dose levels declined from 233 and 254 (21 days after dose 2) to 55 and 87 at month 3, respectively, and to 16 and 27 at month 6, respectively. In older participants, nAb GMTs declined from 80 and 160 (21 days after dose 2) to 10 and 21 at month 6. Overall, higher antibody titers were observed in younger participants, and the 30 µg dose induced higher levels of nAb, which declined more slowly by month 6. No serious adverse events were reported in the vaccine group.
Wei et al.	Identification and application of a neutralizing epitope within alpha-hemolysin using human serum antibodies elicited by vaccination	Clinical Trial 2021	collected sera from volunteers in a phase 1b clinical trial of a novel recombinant five-antigen SA vaccine (NCT03966040). Using a Luminex-based assay, we characterized the human serologic response against Hla, and identified Hla121-138 as a neutralizing epitope. In addition, we successfully produced ferritin nanoparticles carrying the neutralizing Hla121-138 epitope (EpNP) in E. coli. EpNP presented as homogenous nanoparticles in an aqueous solution. Immunization with EpNP elicited potent hemolysis-neutralizing antibodies and conferred significant protection in a mouse model of SA skin infection.	Data suggest that EpNP, carrying the neutralizing epitope Hla121-138, is a good candidate for a vaccine against SA.

CONCLUSIONS

Vaccination has had a major impact on the control of infectious diseases. Older vaccines, including those that successfully prevent measles and polio, work by stimulating the body's immune system and antibody production using a dead or weakened (attenuated) pathogen. However, in someone with a compromised immune system, an attenuated pathogen may still cause the disease, and a dead pathogen may not result in a

strong enough or long-lasting immune response. Many of these vaccines have been shown to elicit protective immunity against many diseases, but they are associated with certain challenges that limit their effectiveness in a clinical setting. DNA and RNA vaccines, for example, are cost-effective and associated with minimal infection risks but can be easily degraded as a result of delivery challenges to target sites. nanoscale size (<1000 nm) materials such as virus-like particles, liposomes, ISCOMs, polymeric, and non-degradable nanospheres

have received attention as potential delivery vehicles for vaccines. The vaccine antigen is either encapsulated within or decorated onto the surface of the NP. By encapsulating antigenic material, NPs provide a method for delivering antigens that may otherwise degrade rapidly upon injection or induce a short-lived, localized immune response. In this review, we assess the potential of these delivery systems for the creation of new vaccines against a variety of infections and compare the usefulness of various NP systems for the delivery of subunit vaccines. The effectiveness of vaccines is determined in large part by a number of physicochemical characteristics of nanoparticles. Clinical Trial Studies have shown that nanocarriers can function as effective middlemen in the creation of vaccinations against a variety of diseases. Development of NP formulations that can deliver immunogens to APCs, particularly DCs, is crucial in this situation to promote efficient antigen-specific T-cell responses. Via B-cell receptors, B cells are able to identify and react to microbial surface antigens. For the creation of vaccines against various diseases, artificial NPs have been used to activate and clonally expand antigen-specific B-cells. Comparing the delivery of exposed vaccine molecules to the encapsulation of antigens in virus-like particles (VLPs), studies found that the VLPs were able to elicit robust and long-lasting humoral responses. Several research clearly proved the effectiveness of non-invasively given vaccines. Concerns about particle toxicity, production challenges, and delivering antigens in their natural state are just a few of the difficulties of using NPs for vaccine administration. Future research on Nano vaccines will focus on the action of NPs as well as the potential to elicit an immune response for the treatment of diseases.

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